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(71) Applicant *(for all designated States except US)*: ISIS INNOVATION LIMITED [GB/GB]; 2 South Parks Road, Oxford OX1 3UB (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TERRAR, Derek [GB/GB]; 9 Oxford Road, Woodstock, Oxfordshire OX20 1UN (GB). GILL, Edward [GB/GB]; 6 Cavendish Road, Oxford OX2 7TW (GB). MAMAS, Mamas [GB/GB]; 36 Gatley Road, Cheadle-Cheshire, Stockport SK8 7QG (GB).

(74) Agent: PENNANT, Pyers; Stevens Hewlett & Perkins, 1 Serjeants' Inn, Fleet Street, London EC4Y 1LL (GB).

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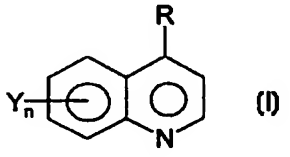

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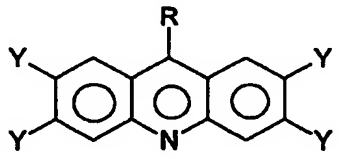

(II)

(57) Abstract

Compounds having formula (I) or (II) where R is primary or secondary amine or a group –L–Z, Y is H, halogen, alkyl, alkoxy, perfluoroalkyl, nitro or –L–Z, n is 1 to 4, L is a linker chain of 1–20 C, N, O or S atoms, and Z is a calcium channel blocker; have potassium channel blocking activity and are useful for the prophylaxis or therapy of arrhythmia.

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ANTIARRHYTHMIC AGENTS

As a result of the outcome of a cardiac arrhythmia suppression trial in 1989, the search for drugs controlling reentrant ventricular tacyarrhythmias and sudden death has focused on agents that prolong the cardiac action potential and refractoriness (i.e. drugs that possess class III antiarrhythmic action). The prototype class III antiarrhythmic drugs currently in clinical use are amiodarone and sotalol. However amiodarone has a complex pharmacological profile and its precise mechanism of action is unclear; and sotalol, in addition to prolonging action potential duration, is a β adenoreceptor antagonist that may cause cardiac depression and negative inotropism.

Selective block of cardiac potassium current will prolong action potential duration and hence the refractory period, an effect believed to contribute to the antiarrhythmic actions of existing drugs derived from sotalol derivatives. However, prolongation of action potential duration in such a manner may be pro-arrhythmic under certain conditions occurring as a result of disturbances of calcium balance in the heart. In consequence, one group has sought to develop an antiarrhythmic agent that shows both calcium channel and potassium channel blocking activity (A Bril *et al*, J Pharmacol. Exp. Ther. 276 (2), 637-646 (1996)).

This invention results from the discovery of a family of compounds which show potassium channel blocking activity and which are structurally quite different from previous compounds known to have this property. Some compounds have been modified by the attachment of known groups having calcium channel blocking activity, and properties of these modified compounds are reported.

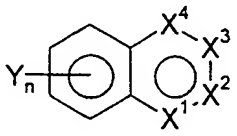
The invention provides, for use as a potassium

channel blocker, a compound comprising a planar electron-deficient ring structure of at least two fused 6-membered rings containing at least one ring N atom.

Ring structures of two or more fused 6-membered rings are generally planar or achiral as a result of having aromatic unsaturation. This ring structure may have substituents that extend out of the plane of the ring system; but comparable ring systems that are not planar do not appear to have potassium channel blocking activity.

The presence in the system of at least one ring N atom makes or tends to make the ring structure electron-deficient. But this effect may not be shown, or not sufficiently shown by the simple unsubstituted ring structure. The effect is greatly accentuated if the ring N atom is itself substituted. The effect is greatly accentuated by the presence, *ortho* or *para* to a ring N atom, of an electron-withdrawing substituent.

Preferred compounds are based on quinoline and acridine. On the fused ring structures of these compounds may be bonded substituents designed to perform various functions: to increase the electron deficiency of the ring structure; to provide calcium channel blocking activity; to enhance the lipophilic or hydrophilic properties; to provide a zero or positive or negative charge on the compound as a whole. Preferred compounds have the formula



where 1,2 or 3 of X^1, X^2, X^3 and X^4 are N or $\equiv N^+$-Q and each remaining X^1, X^2, X^3 and X^4 is $\equiv C$-Y,

Q is optionally substituted alkyl,

Y is H, halogen, primary, secondary or tertiary amine,

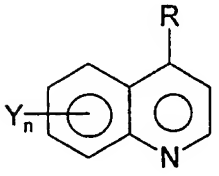
optionally substituted alkyl , alkoxy or perfluoroalkyl, nitro or a group -L-Z; or two adjacent Y may be joined together to form a carbocyclic ring,

L is a linker chain of 1-20 C, N, O or S atoms,

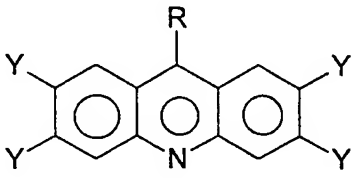
Z is a calcium channel blocker,

and n is 1 to 4.

Preferably a primary or secondary amine group is attached to the ring structure at a position *para* to a ring N atom. Particularly preferred compounds of this type have the formula



or



where R is primary or secondary amine or a group -L-Z,

Y and n are as previously defined.

Preferred compounds have a group -L-Z which provides calcium channel blocking activity These are included as new compounds within the scope of the invention. Preferably L is $-NH(CH_2)_3N(CH_2)_2-$ and Z is phenyl or 3,4-dimethoxyphenyl. Such groups are well known and described in the literature. See R Mannhold *et al*, Archives of Pharmacology, 1978, **302** 217-226.

The compounds are expected to be useful for the prophylaxis or therapy of arrhythmia, for which purpose they are expected to be injected into the blood stream. They will also be useful as experimental tools to separate components of the potassium current in a variety of tissues. These uses constitute further aspects of the invention.

Reference is directed to the accompanying drawings, in which Figures 1-6, 8-12 and 14 are graphs of various effects against time,

and Figures 7 and 13 show compound structures.

Figure 1 shows the effect of 5mM E4031 on I_K. **A**. Mean data from 7 cells before (filled circles) and after (empty circles) exposure to E4031. **B**. E4031 sensitive currents. I_K was activated by step depolarisations from -40mV to +40mV for 10 to 800 ms and were measured as outward tails upon repolarisation to -40mV (switch voltage clamp; 36°C) in the presence of cytosolic BAPTA to suppress calcium transients. A similar protocol was adopted in all subsequent experiments where I_K was investigated (see Heath & Terrar, 1996, Experimental Physiology, **81**, p587-603).

Figure 14 illustrates the log(dose)-response curve of I_{KR} and I_{Ca} inhibition by GT96/1,2,3&4. I_{Ca} was activated by step depolarisations from -40mV to 0 mV for 200ms (switched voltage clamp). I_K was activated by step polarisations from -40mV to +40mV for 10-800ms (switched voltage clamp) and measured as outward tails upon repolarisation to -40mV; current at 40 ms was taken to represent I_{Kr} (see Heath & Terrar, 1996, Experimental Physiology, **81**, p587-603).

EXPERIMENTAL

The delayed rectifier potassium current (I_K) is one of the major time and voltage dependent outward potassium currents in heart cells, it plays an important role in the repolarisation of cardiac action potentials. Two components of I_K have been separated and can be distinguished by their differing kinetics and pharmacology. The rapidly activating component (I_{Kr}) exhibits rapid activation, being maximal within 50ms and is sensitive to the class III antiarrhythmic drug E4031. The more slowly activating component (I_{KS}) exhibits a slower, sigmoidal activation and even at very long and very positive potentials it does not become maximally activated. This component is sensitive to the general anaesthetics propofol and thiopentone.

EXAMPLE 1

Using the known class III antiarrhythmic drug E4031 which is believed to be a selective blocker of I_{Kr}, the two components of the delayed rectifier potassium current can be separated. Figure 1A illustrates that following exposure of guinea pig isolated ventricular heart cells to 5μM E4031, a reduction in I_K was observed, especially I_K activated by short pulses of less than 200ms. Since E4031 is reported to selectively block I_{Kr}, the current remaining in the presence of E4031 represents I_{Ks} and in accordance with this, the drug-insensitive I_K is slow to activate and exhibits a sigmoidal activation. Subtraction of the E4031 insensitive current from control current produced the E4031-sensitive current, or I_{Kr} (Figure 1B), exhibiting a rapid activation, being maximal within 50ms.

The actions of E4031 on I_K illustrated in Figure 1A are representative of a typical response to a selective I_{Kr} blocker, and similar actions on I_K were recorded with the novel I_{Kr} blockers of this invention.

The initial experiments which led to the characterisation of the novel chemical group exhibiting I_{Kr} blocking activity followed from the observations that exposure of guinea pig isolated ventricular heart cells to methylene blue (10 μM), an inhibitor of the cytosolic enzyme guanylate cyclase, enhanced cell contraction amplitude (Figure 2A), with an associated increase in action potential duration. These actions appeared not to be related to the inhibition of guanylate cyclase activity since exposure of cells to a structurally dissimilar guanylate cyclase inhibitor, LY83583 (10 μM) did not produce such responses (Figure 2B). The prolongation of action potential duration and hence increase in cell contractility observed following exposure to methylene blue was not associated with effects on either L-type calcium currents (Figure 3) or inwardly rectifying potassium currents (Figure 4). In contrast, a decline in the rapidly activating component of the delayed rectifier potassium current was observed following exposure to 10 μM methylene blue (Figure 5). The

structurally dissimilar guanylate cyclase inhibitor LY83583 (10 μM) had no effects on I_{Kr} (Figure 6), it therefore seems likely that methylene blue inhibits I_{Kr} through a direct action on the channel rather than through inhibition of guanylate cyclase activity. Further support for such a view is that compounds such as quinacrine (Figure 7), chloroquine (Figure 7) and 9-aminoacridine (Figure 7), which do not exhibit guanylate cyclase inhibiting activity, but possess a flat planar electron deficient ring structure similar to that of methylene blue (Figure 7) also exhibit potent I_{Kr} blocking activity (Figure 8). In a separate set of experiments the inventors have also investigated the I_{Ks} blocking activity of one of these compounds, 9-aminoacridine which appears to be negligible at 10 μM, demonstrating that these compounds are selective for I_{Kr}. In the next set of experiments the inventors investigated whether the positive charge and/or the flat planar structure of such compounds is required for I_{Kr} blocking activity. Acridine hydrochloride (Figure 7) possesses a flat planar electroneutral ring structure but did not exhibit I_{Kr} blocking activity (Figure 9). In contrast the structurally similar methylacridine sulphonate (Figure 7) which possesses a weakly positively charged flat planar ring structure exhibited I_{Kr} blocking activity (Figure 10); hence it appears that an electron deficient ring structure is required for I_{Kr} blocking activity. 9-aminotetrahydroacridine (Figure 7) has 2 unsaturated electron deficient rings which lie in the same plane (although the saturated ring introduces a kink at the end of the compound) and this exhibits I_{Kr} blocking activity (Figure 11). In contrast 1,2,3,4-tetrahydroquinoline (Figure 7) does not possess a flat planar structure and although it is electron deficient it does not exhibit I_{Kr} blocking activity (Figure 12); hence it appears that at least 2 rings must lie in a plane and that this flat planar portion of molecule must be electron deficient for a compound to exhibit I_{Kr} blocking activity.

EXAMPLE 2

In addition the inventors have synthesised a novel set of compounds which incorporate both the chemical group exhibiting I_{Kr} blocking activity and an additional chemical group conferring calcium channel blocking activity (Figure 13). Both the calcium channel and potassium channel blocking activity has been investigated in these newly synthesised compounds (Figure 14). Compound GT96/4 appears to show the greatest difference in potency between block of I_{Kr} and of calcium channels.

Antiarrhythmic Properties of GT 96/4

Guinea-pig hearts were mounted on a Langendorff apparatus, and perfused through the aorta with a solution at pH 7.4, 36°C as described in Heath B M and Terrar D A, Experimental Physiology, Vol 81, p 587-603 (1996). Ischaemia was induced by stopping the inflow of perfusing solution for 30 minutes. Arrhythmias were provoked following reperfusion. Arrhythmias were quantified by:-

- taking a signal from a tension transducer (attached to the heart by a hook at its apex and therefore measuring ventricular contraction), and
- feeding this signal to a device which measured the interval between contractions (the reciprocal of heart rate).

The output of this device was proportional to the interval between beats so that a steady level reflected a steady rate and fluctuations in this level reflected disturbances in rhythm. The possible effect of novel compounds on arrhythmias was tested by switching the inflow of the perfusion apparatus to a solution containing the compound of interest GT 96/4, at 10^{-7}M. Reversibility of effect was tested by switching back to drug-free solution.

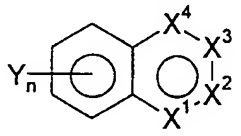
Arrhythmia was quantified from a recording of the intervals between heart contractions in such a manner that a large variation in rhythm gave rise to a large value (arbitrary units). Results are reported below.

Test Condition	Level of Arrhythmia (arbitrary units)			Mean Values
Base induced arrhythmia	21	25	23	23
Arrhythmia during drug treatment	1	1	6	2.67
Arrhythmia post drug washout	23	23	-	23

CLAIMS

1. For use as a potassium channel blocker, a compound comprising a planar electron-deficient ring structure of at least two fused 6-membered rings containing at least one ring N atom.

2. A compound as claimed in claim 1 having the formula



where 1,2 or 3 of X^1, X^2, X^3 and X^4 are N or $\equiv N^+$-Q and each remaining X^1, X^2, X^3 and X^4 is $\equiv$C-Y,

Q is optionally substituted alkyl,

Y is H, halogen, primary, secondary or tertiary amine, optionally substituted alkyl , alkoxy or perfluoroalkyl, nitro or a group -L-Z; or two adjacent Y may be joined together to form a carbocyclic ring,

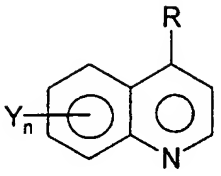
L is a linker chain of 1-20 C, N, O or S atoms,

Z is a calcium channel blocker,

and n is 1 to 4.

3. A compound as claimed in claim 1 or claim 2, wherein a primary or secondary amine group is attached to the ring structure at a position *para* to a ring N atom.

4. A compound as claimed in claim 3 having the formula



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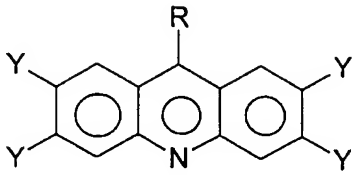


where R is primary or secondary amine or a group -L-Z,

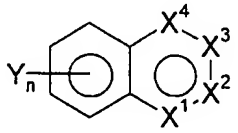
Y and n are as previously defined.

5. A compound as claimed in claim 4, wherein Y is H, chloro, primary or secondary amine or methoxy or the group -L-Z, and L is a linker chain of 1-20 carbon atoms, optionally including one or more O, N or S atoms.

6. A compound as claimed in claim 4 or claim 5, wherein R is -L-Z..

7. A compound as claimed in any one of claims 2 to 6, wherein L is $-NH(CH_2)_3N(CH_3)(CH_2)_2-$ and Z is phenyl or 3,4-dimethoxyphenyl.

8. A compound having the formula:



where 1,2 or 3 of X^1, X^2, X^3 and X^4 are N or $\equiv N^+$-Q and each remaining X^1, X^2, X^3 and X^4 is $\equiv C$-Y,

Q is optionally substituted alkyl,

Y is H, halogen, primary, secondary or tertiary amine, optionally substituted alkyl , alkoxy or perfluoroalkyl, nitro or a group -L-Z; or two adjacent Y may be joined together to form a carbocyclic ring,

L is a linker chain of 1-20 C, N, O or S atoms,

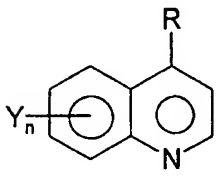
Z is a calcium channel blocker,

and n is 1 to 4,

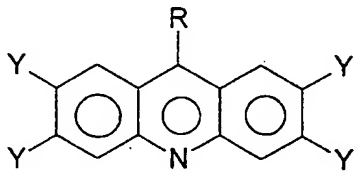
provided that at least one group -L-Z is present.

9. A compound as claimed in claim 8, wherein a primary or secondary amine group is attached to the ring structure at a position *para* to a ring N atom.

10. A compound as claimed in claim 8, having the formula



or



where R is primary or secondary amine or a group -L-Z, Y and n are as previously defined.

11. A compound as claimed in claim 10, wherein Y is H, chloro, primary or secondary amine or methoxy or the group -L-Z, and L is a linker chain of 1-20 carbon atoms, optionally including one or more O, N or S atoms.

12. A compound as claimed in claim 10 or claim 11, wherein R is –L-Z.

13. A compound as claimed in any one of claims 8 to 12, where L is $–NH(CH_2)_3N(CH_3)(CH_2)_2$- and Z is phenyl or 3,4-dimethoxyphenol.

14. A method of preparing an anti-arrhythmic agent, which method comprises bringing a compound as claimed in any one of claims 1 to 12 into a form suitable for administration.

Fig.1A.

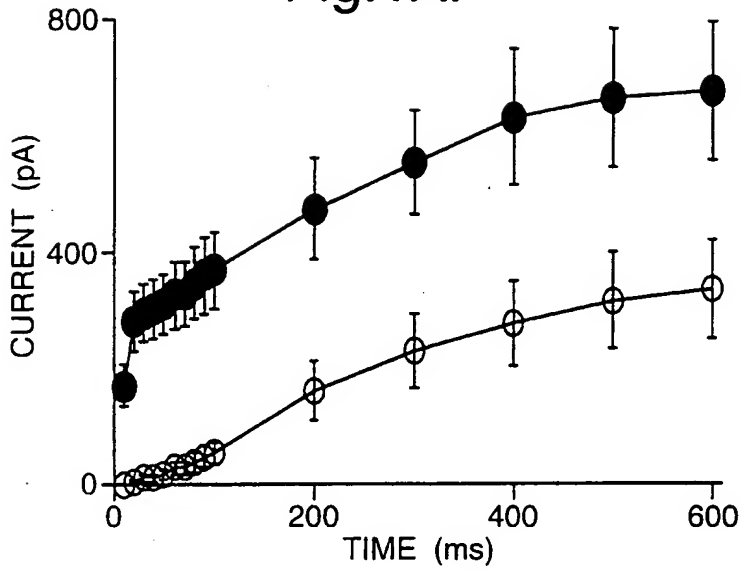
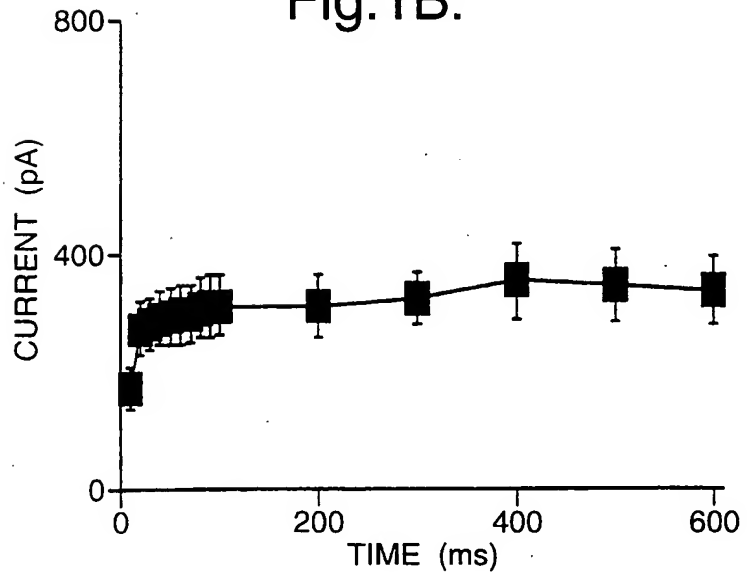

800
400
0
CURRENT (pA)
0
200
400
600
TIME (ms)

Fig.1B.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200
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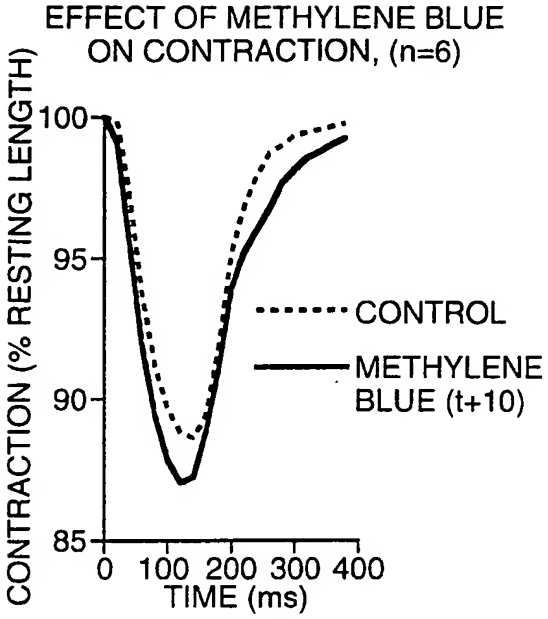
600
TIME (ms)

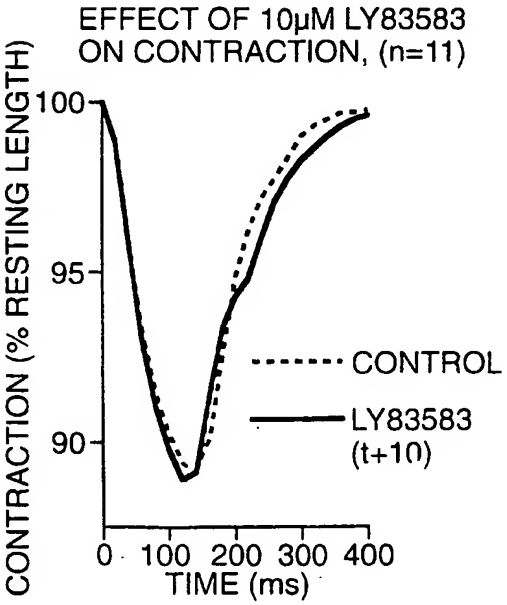
Fig.2A.



ACTION POTENTIAL DATA

	METHYLENE BLUE (t+10)
APD20 (% CONTROL)	140
SE	7
APD90 (% CONTROL)	152
SE	7

Fig.2B.



ACTION POTENTIAL DATA

	LY83583 (t+10)
APD20 (% CONTROL)	104
SE	2
APD90 (% CONTROL)	106
SE	4

Fig.3.

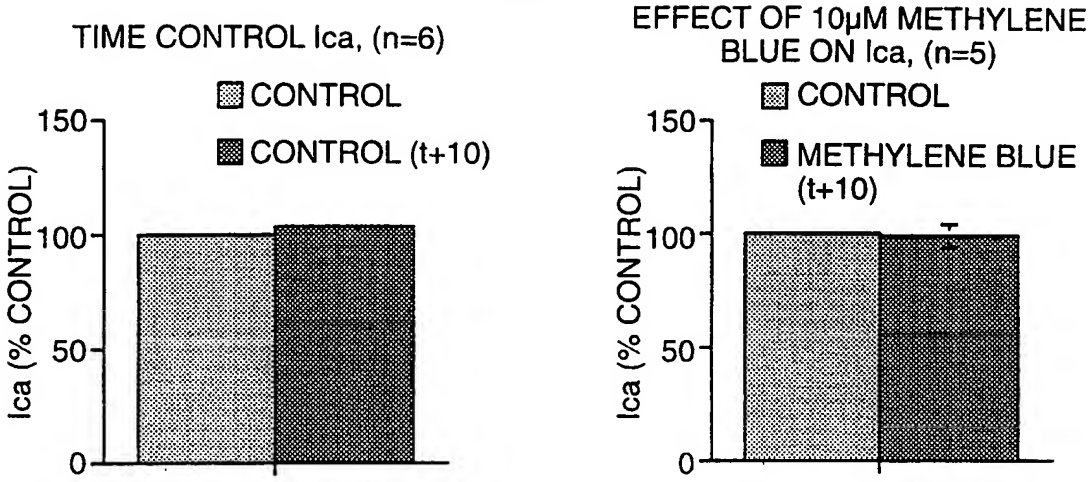

TIME CONTROL Ica, (n=6)
CONTROL
CONTROL (t+10)
Ica (% CONTROL)
150
100
50
0
EFFECT OF 10μM METHYLENE BLUE ON Ica, (n=5)
CONTROL
METHYLENE BLUE (t+10)
Ica (% CONTROL)
150
100
50
0

Fig.4.

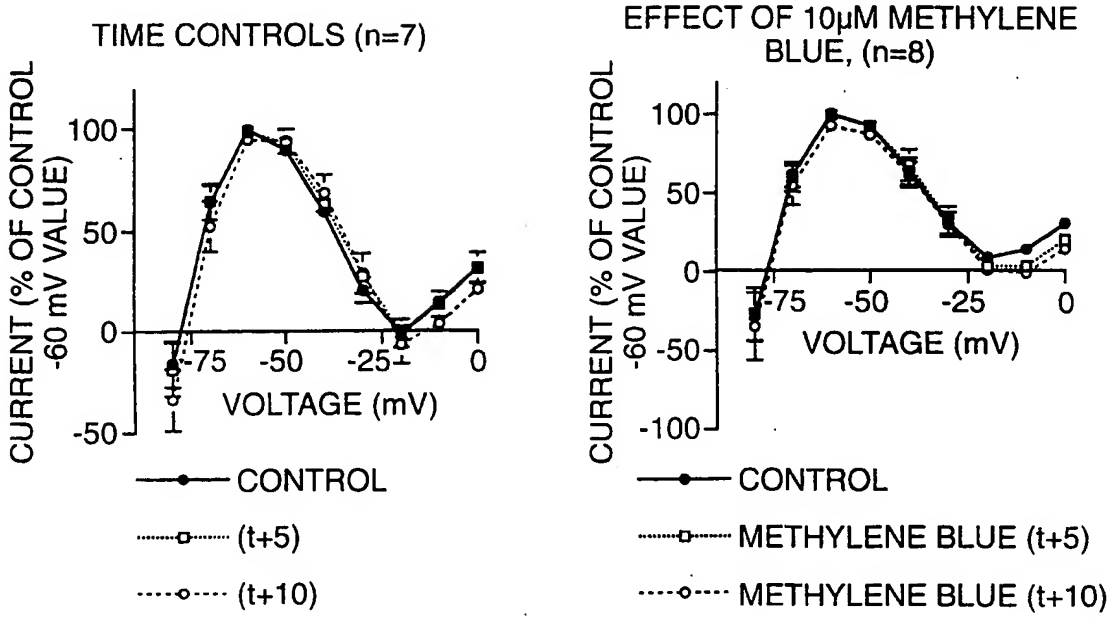

TIME CONTROLS (n=7)
CURRENT (% OF CONTROL -60 mV VALUE)
100
50
0
-50
-75
-50
-25
0
VOLTAGE (mV)
CONTROL
(t+5)
(t+10)
EFFECT OF 10μM METHYLENE BLUE, (n=8)
CURRENT (% OF CONTROL -60 mV VALUE)
100
50
0
-50
-100
-75
-50
-25
0
VOLTAGE (mV)
CONTROL
METHYLENE BLUE (t+5)
METHYLENE BLUE (t+10)

Fig.5.

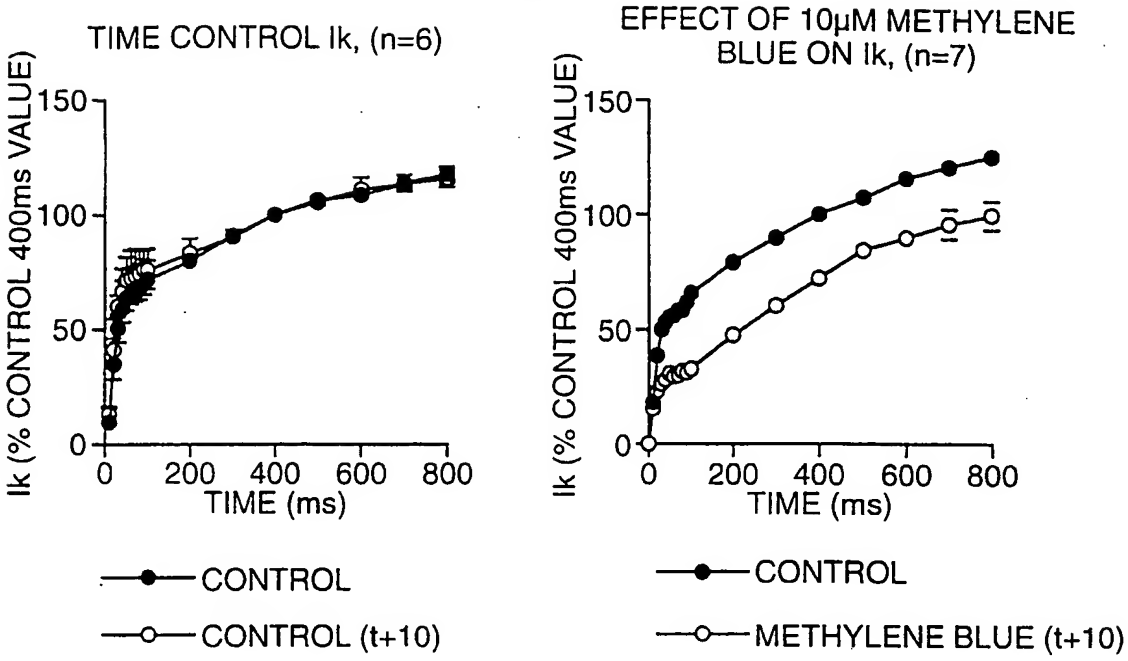

TIME CONTROL Ik, (n=6)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
CONTROL (t+10)
EFFECT OF 10μM METHYLENE BLUE ON Ik, (n=7)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
METHYLENE BLUE (t+10)

Fig.6.

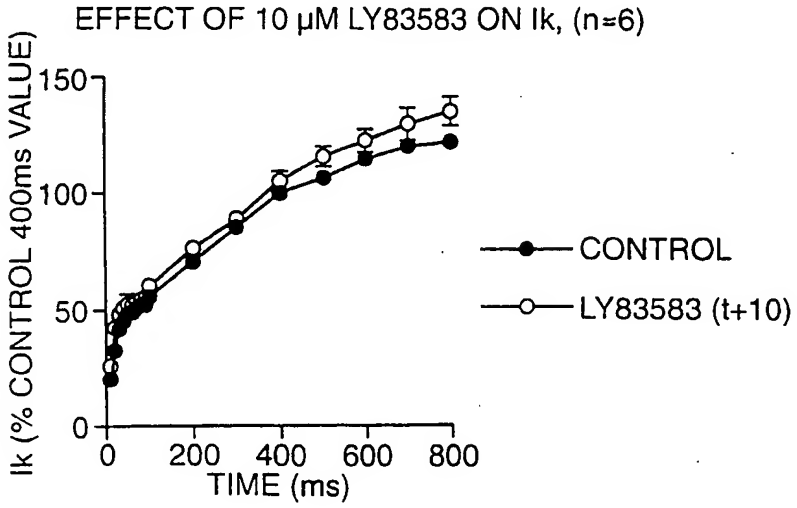
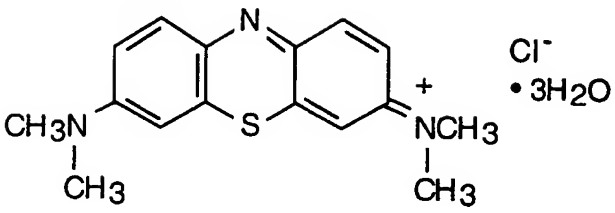
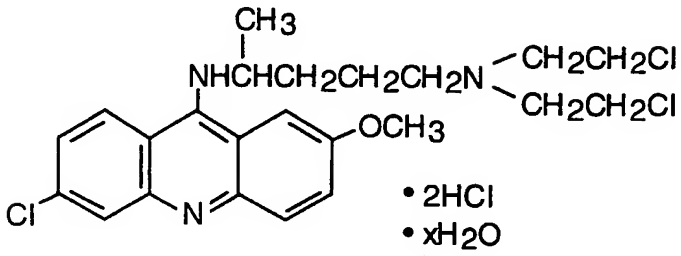

EFFECT OF 10 μM LY83583 ON Ik, (n=6)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
LY83583 (t+10)

Fig.7.

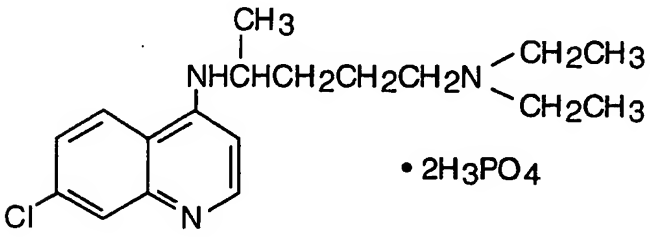
METHYLENE BLUE



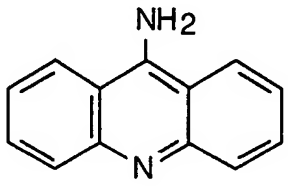
QUINACRINE



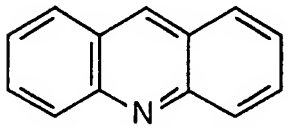
CHLOROQUINE



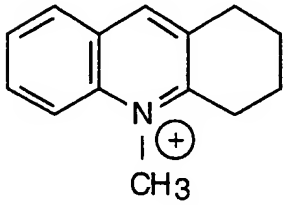
9-AMINOACRIDINE



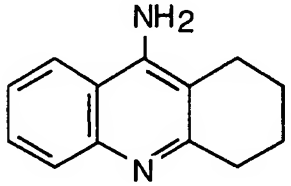
ACRIDINE



METHYACRIDINE



9-AMINOTETRAHYDROACRIDINE



1,2,3,4-TETRAHYDROQUINOLINE

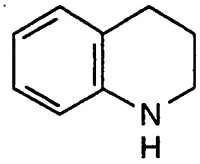
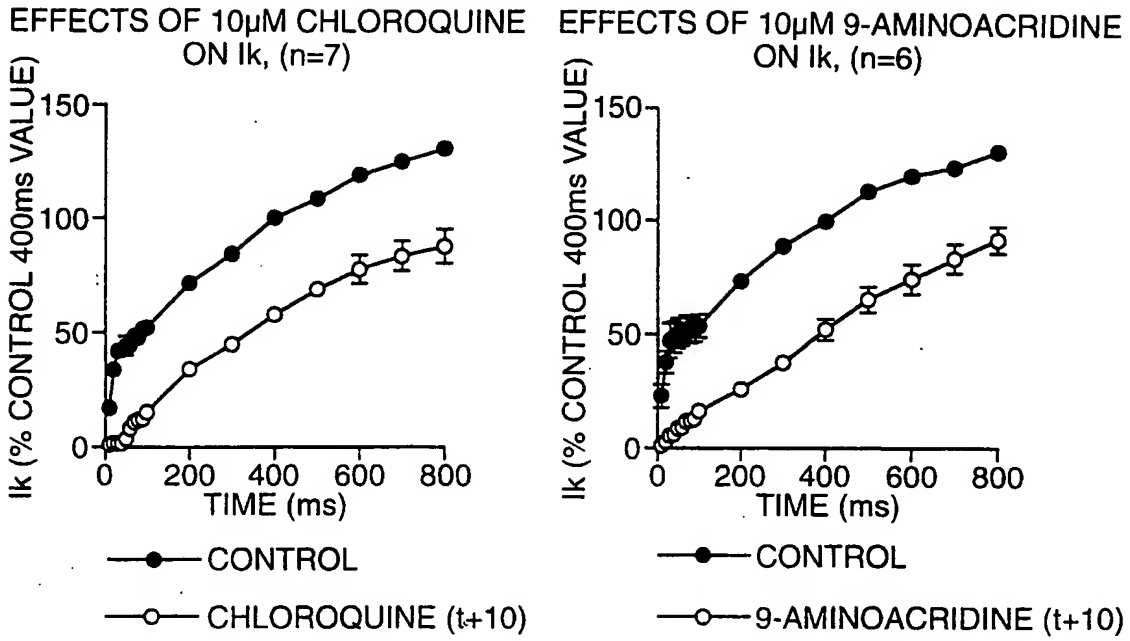


Fig.8.


EFFECTS OF 10μM CHLOROQUINE ON Ik, (n=7)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
CHLOROQUINE (t+10)
EFFECTS OF 10μM 9-AMINOACRIDINE ON Ik, (n=6)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
9-AMINOACRIDINE (t+10)

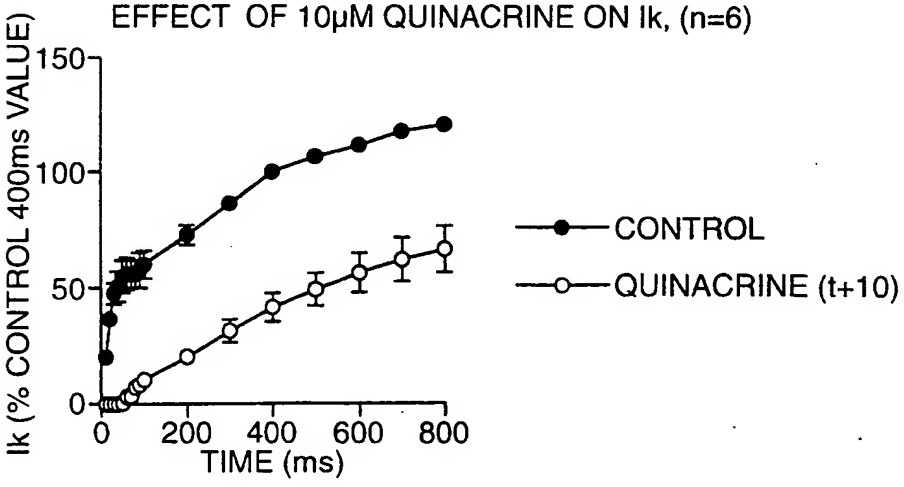

EFFECT OF 10μM QUINACRINE ON Ik, (n=6)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
QUINACRINE (t+10)

Fig.9.

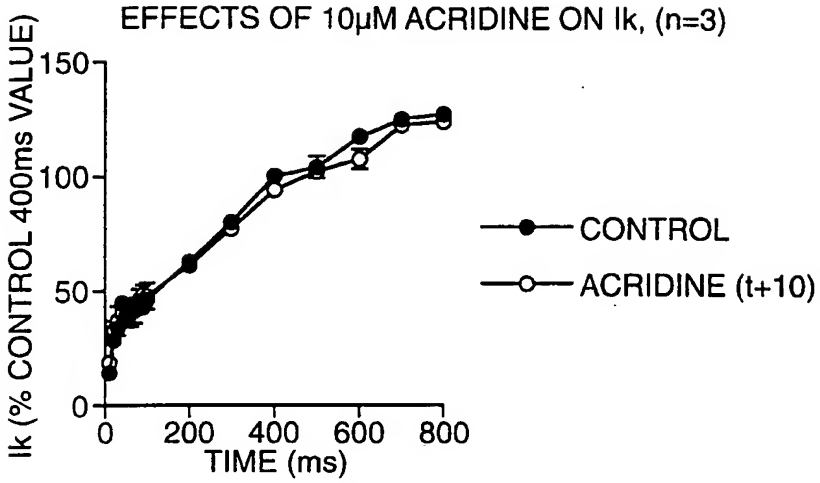

EFFECTS OF 10μM ACRIDINE ON Ik, (n=3)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
ACRIDINE (t+10)

Fig.10.

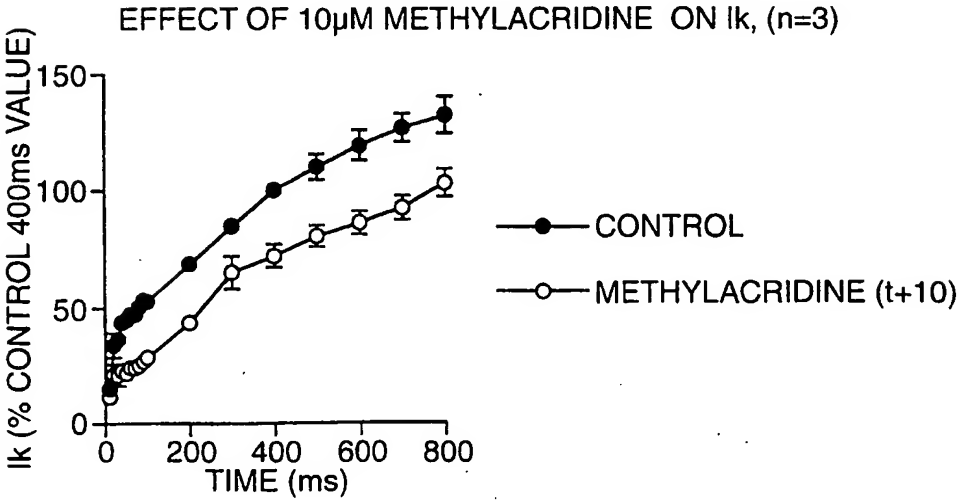

EFFECT OF 10μM METHYLACRIDINE ON Ik, (n=3)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
METHYLACRIDINE (t+10)

Fig.11.

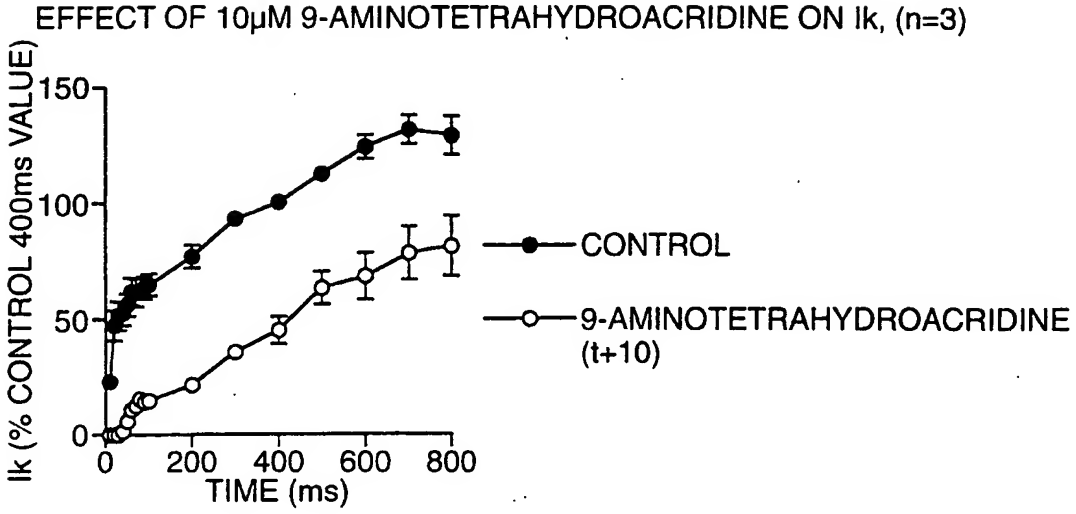

EFFECT OF 10μM 9-AMINOTETRAHYDROACRIDINE ON Ik, (n=3)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
9-AMINOTETRAHYDROACRIDINE
(t+10)

Fig.12.

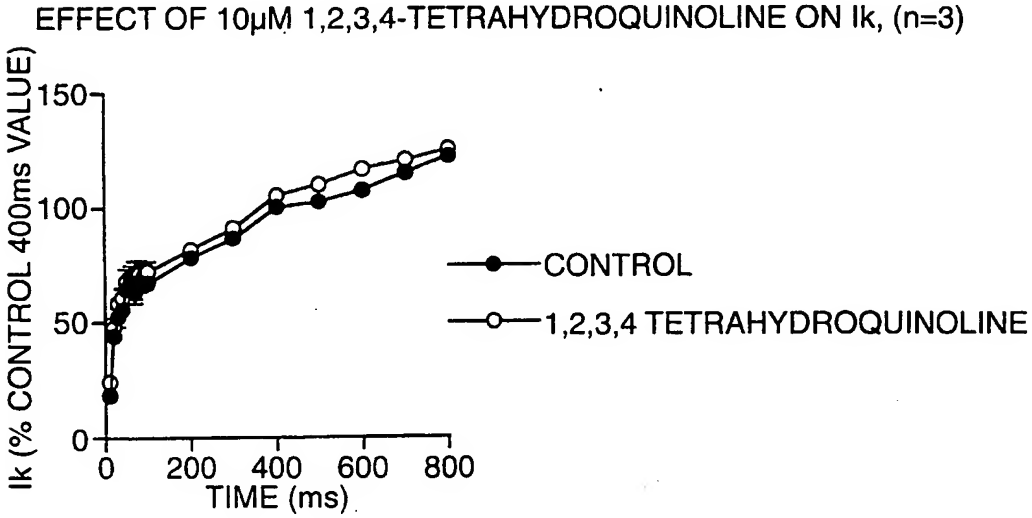
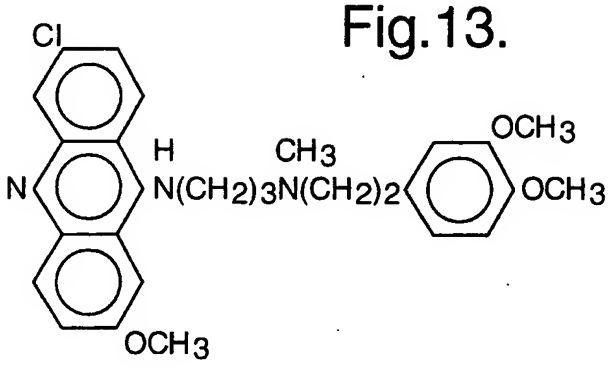
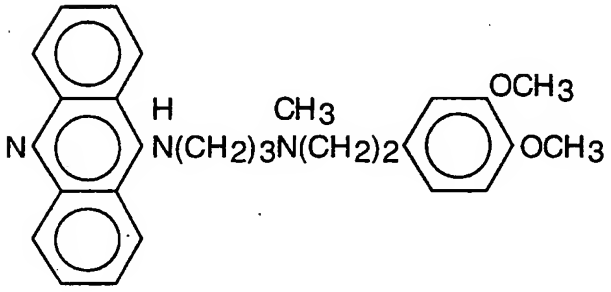

EFFECT OF 10μM 1,2,3,4-TETRAHYDROQUINOLINE ON Ik, (n=3)
Ik (% CONTROL 400ms VALUE)
150
100
50
0
0
200
400
600
800
TIME (ms)
CONTROL
1,2,3,4 TETRAHYDROQUINOLINE

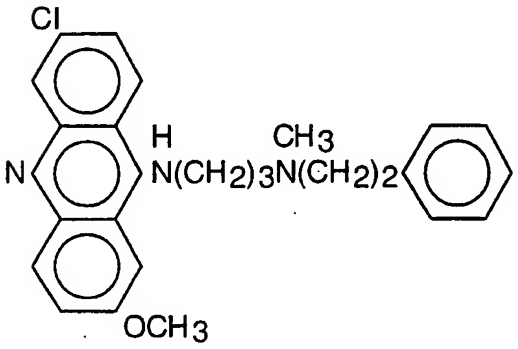
Fig.13.



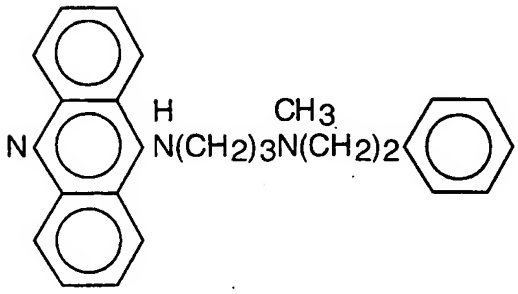
GT96/1



GT96/2

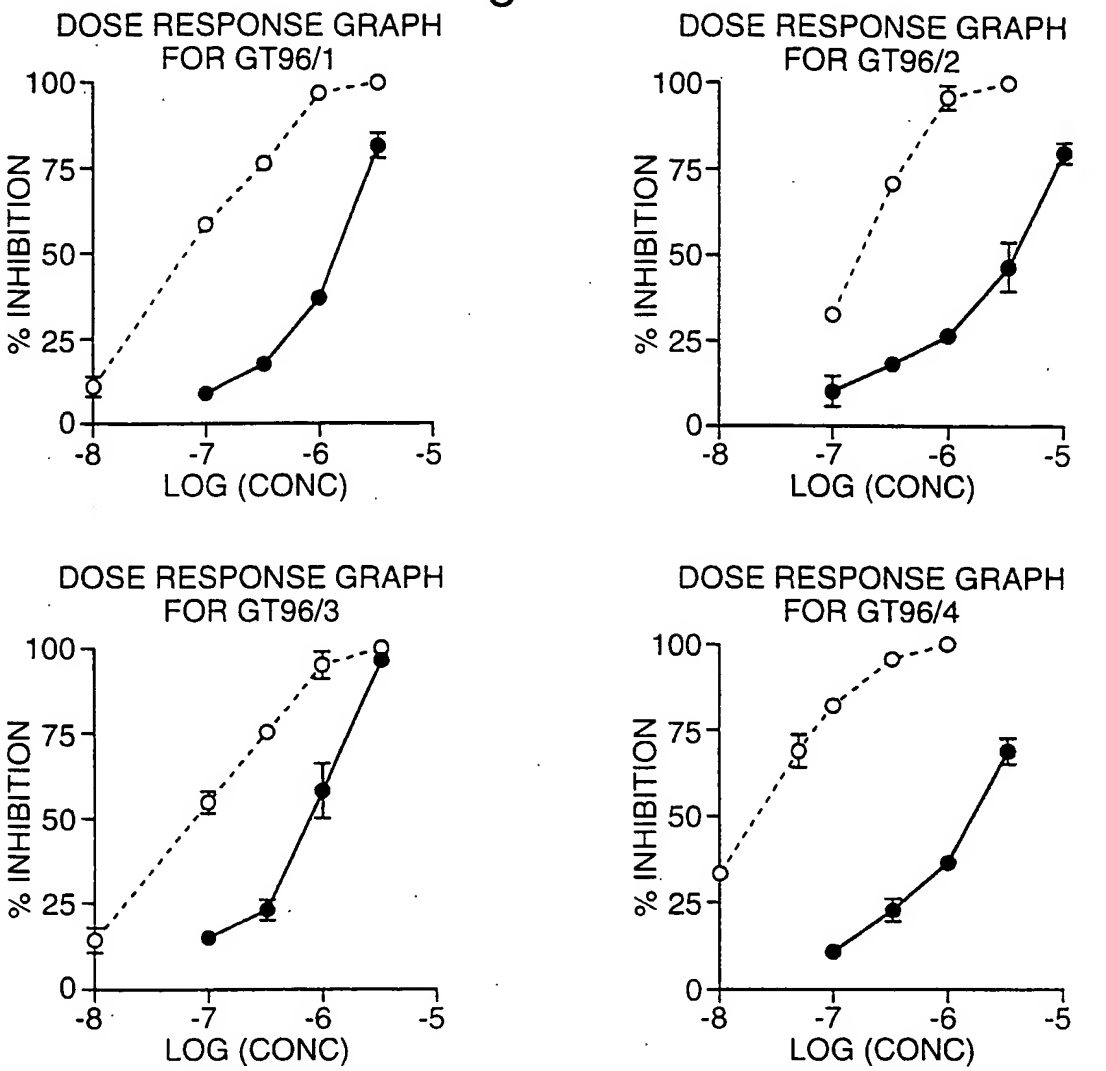


GT96/3



GT96/4

Fig.14.



	IC50 FOR ICa(L)	IC50 FOR IKr
GT96/1	1.4μM	63nM
GT96/2	3.5μM	141nM
GT96/3	795nM	70nM
GT96/4	1.58μM	18.5nM

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: ISIS INNOVATION LIMITED [GB/GB]; 2 South Parks Road, Oxford OX1 3UB (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TERRAR, Derek [GB/GB]; 9 Oxford Road, Woodstock, Oxfordshire OX20 1UN (GB). GILL, Edward [GB/GB]; 6 Cavendish Road, Oxford OX2 7TW (GB). MAMAS, Mamas [GB/GB]; 36 Gatley Road, Cheadle–Cheshire, Stockport SK8 7QG (GB).

(74) Agent: PENNANT, Pyers; Stevens Hewlett & Perkins, 1 Serjeants' Inn, Fleet Street, London EC4Y 1LL (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
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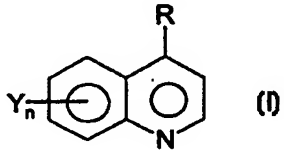
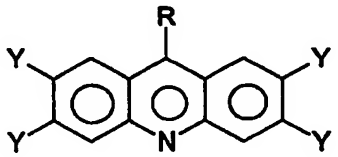
(88) Date of publication of the international search report: 4 March 1999 (04.03.99)

(54) Title: QUINOLINE AND ACRIDINE DERIVATIVES AS ANTIARRHYTHMIC AGENTS



(I)



(II)

(57) Abstract

Compounds having formula (I) or (II) where R is primary or secondary amine or a group –L–Z, Y is H, halogen, alkyl, alkoxy, perfluoroalkyl, nitro or –L–Z, n is 1 to 4, L is a linker chain of 1–20 C, N, O or S atoms, and Z is a calcium channel blocker; have potassium channel blocking activity and are useful for the prophylaxis or therapy of arrhythmia.

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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 98/01579

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/42 C07D219/10 C07D215/46 C07D219/12 A61K31/47

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 446 604 A (AMERICAN CYANAMID CO) 18 September 1991 see page 41; claim 8 ---	1-6, 8-12,14 7,13
X	DATABASE WPI Section Ch, Week 9615 Derwent Publications Ltd., London, GB; Class B02, AN 96-151305 XP002076733 & WO 96 06084 A (C & C RES LABS)	1-6, 8-12,14
Y	see abstract ---	7,13
X	US 3 957 791 A (SIMPSON WILLIAM R) 18 May 1976 see column 4, line 21 - line 27 ---	1-6, 8-12,14
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of theinternational search	Date of mailing of the international search report
8 September 1998	25.09.98

Name and mailing address of the ISA	Authorized officer
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3

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 98/01579

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 534 844 A (ROUSSEL UCLAF) 31 March 1993 see page 5, line 36 - line 38	1-6, 8-12,14
X	EP 0 242 173 A (PFIZER LTD) 21 October 1987 see claim 1	1,2,8,14
X	EP 0 281 254 A (PFIZER LTD) 7 September 1988 see claim 1	1,2,8,14
X	DATABASE WPI Section Ch, Week 9610 Derwent Publications Ltd., London, GB; Class B02, AN 96-094177 XP002076734 & JP 08 003 144 A (CHUGAI PHARM CO LTD) see abstract	1-6, 8-12,14
X	CHEMICAL ABSTRACTS, vol. 119, no. 15, 11 October 1993 Columbus, Ohio, US; abstract no. 151891t, REES ET AL.: "Tacridine inhibits ventricurla fibrilation..." XP002076731 & Cardiovasc. Res. 1993 27(3), 453-458 see abstract	1-5, 8-11,14
A	CHEMICAL ABSTRACTS, vol. 89, no. 3, 17 July 1978 Columbus, Ohio, US; abstract no. 16708k, MANNHOLD ET AL.: "Investigations on the structure-activity relationships of verapamil" XP002076732 & Arch. Pharm. 1978 302(2), 217-226 see abstract	1-14
X,P	WO 97 23462 A (PFIZER RES & DEV ;PFIZER LTD (GB); PFIZER (US); COLLIS ALAN JOHN () 3 July 1997 see page 13, line 7	1-6, 8-12,14
E	EP 0 847 996 A (HOECHST AG) 17 June 1998 see the whole document	1-6, 8-12,14

3

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/01579

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-6,8-12,14
because they relate to subject matter not required to be searched by this Authority, namely:

see below

2. [X] Claims Nos.: 1-6,8-12,14
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-6,8-12,14

In view of the large number of compounds, which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons.
Moreover, the definition of Z as a calcium channel blocker is obscure.
The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/GB 98/01579

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		PT 86702 B	30-04-1992
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/GB 98/01579

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0847996 A	17-06-1998	DE 19652213 A	18-06-1998
		AU 4837397 A	18-06-1998
		CN 1185435 A	24-06-1998
		JP 10182610 A	07-07-1998
		NO 975887 A	17-06-1998
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